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Serologic Evolution of Neurocysticercosis Patients after Antiparasitic Therapy

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Abstract

Neurocysticercosis is the main cause of acquired epilepsy in developing countries and is an emerging disease in the United States. Introduction of the immunoblot assay provided a new tool for the diagnosis and monitoring of neurocysticercosis. This study analyzed the relationship between clinical characteristics of cerebral infection (number and type of lesions) plus the baseline response on immunoblot and the changes observed after therapy. Reaction to all 7 diagnostic bands was associated with severe infection (more lesions). Seventeen patients (35%) had no active lesions on computed tomography (CT) 3 months after therapy and were considered cured. Although most cured patients remained seropositive after 1 year, 3 became seronegative before 9 months. In these 3 cases, the lesions had resolved on CT at 3 months. Persistent seropositivity does not necessarily indicate active infection. Serologic follow-up will be clinically helpful only in rare cases in which early antibody disappearance occurs.

Neurocysticercosis (NCC), the infection of the central nervous system by the larvae of *Taenia solium*, is the main cause of late-onset epilepsy in developing countries [1, 2]. In the United States, due to increased immigration and improved detection through computed tomography (CT) and serology, the prevalence of NCC is increasing every year [3], and it is considered an emerging disease. Antiparasitic therapy with albendazole or praziquantel leads to resolution of most parasitic cysts, although complete cure is achieved in only 35%–65% of patients [4]. CT and magnetic resonance imaging are the only available indicators of therapeutic success [4, 5], but they are expensive and require sophisticated equipment, which is scarce in areas with endemic *T. solium*.

The development of an immunoblot assay for *T. solium* antibodies [6] provided a reliable test for the diagnosis of NCC. There are few data on how infection-specific antibodies, identified on immunoblot, relate to the characteristics of cerebral cysticercosis. In contrast to other serologic tests, immunoblot is useful in studying selective immune response to individual antigens [6] and may be useful for monitoring patient immune responses after treatment. This was not possible with previous serologic tests. We used the immunoblot assay to follow a cohort ofNCC patients for 1 year after albendazole treatment in order to

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Informed consent was obtained from all patients, and the study was approved by the ethical review boards of the Universidad Peruana Cayetano Heredia and Johns Hopkins University.

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describe their baseline serologic responses, the changes after therapy, and the relation of these changes to treatment efficacy.

Materials and Methods

Fifty-five NCC patients from different clinics in Lima, Peru, were consecutively included in a randomized, double-blind study [6a] designed to evaluate two regimens of albendazole therapy. One “pilot” patient treated openly is also included, for a total of 56 cases. NCC patients were diagnosed on the basis of cerebral CT scans showing active lesions (live cysts with or without contrast enhancement or enhancing lesions [1]) and a positive immunoblot. Cysticerci initially appear on CT as cystic lesions (live cysts, rounded, hypodense vesicles, sometimes showing a hyperdense scolex); during their evolution, they become isodense with the cerebral parenchyma, appearing only after the injection of contrast material as annular or nodular structures (colloidal or enhancing lesions). Later they disappear or leave a small calcified scar [7].

Immunoblot tests were done as described [6]. In brief, this assay uses 7 purified *T. solium* glycoprotein antigens (diagnostic bands GP50, GP42–39, GP24, GP21, GP18, GP14, and GP13) in an immunoblot format to detect infection-specific antibodies. Reactions to at least 1 band are considered positive.

Stool microscopy was done to detect intestinal *T. solium* carriers, and patients received a single oral dose of 2 g of niclosamide before albendazole therapy. Albendazole was given orally, 400 mg twice daily for 7 or 14 days. Both groups received steroids for 7 days. Serology was done before albendazole treatment and 7 and 14 days, 3, 6, and 9 months, and 1 year after treatment. Most patients ($n = 32$) also had serology performed at > 1 year. Serology was done more frequently during the first month to determine the effect of therapy on antibody response. It is hypothesized that therapy damages cysticerci and exposes parasitic antigens, thereby inducing antibody production [8].

In 19 cases, results of an immunoblot assay were missing. Since the preceding and following assays had identical results, the missing samplewas assumed to have the same number of bands. Three patients did not have a l-year immunoblot result but had samples taken at later dates (positive in all 3 cases). These cases were considered seropositive at 1 year but were not analyzed for the number of bands.

Efficacy of therapy was assessed by CT 3 months and 1 year after therapy. Patients whose follow-up CT scans showed no active lesions (cysts or enhancing lesions) were considered cured. Patients were included for analysis if they completed 3 months of follow-up, including CT and immunoblot.

Statistical analysis

χ^2 and Fisher’s exact tests were used to analyze associations between discrete variables, and Student’s *t*, the Mann-Whitney, or the Kruskal-Wallis one-way analysis of variance test was used to compare differences between continuous variables. Friedman’s test was used to evaluate changes in the number of bands over time.

Results

Of the original 56 patients, 5 did not complete the 3 months of evaluation: 1 refused to continue, 2 did not return after the day 30 visit, in 1 the medication was given incorrectly, and in 1 the scans were lost. Two other patients had CT evaluations but not immunoblot tests at 3 months. Forty-nine (88%) were finally included in the analysis.

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The patients' age range was 15–77 years (median, 37.0; interquartile range [IQR], 23–49.5). The sex distribution was about equal: 27 men (55%) and 22 women (45%).

Type and number of lesions on CT

Twenty-eight patients (57%) had only cystic lesions, 9 (18%) had only enhancing lesions, and 12 (25%) had both types of lesions. The median number of lesions was 2.0 in patients with only cystic lesions (range, 1–180; IQR, 1.0–4.75), 5.0 in patients with only enhancing lesions (range, 1–23; IQR, 2.5–16), and 8.0 in patients with both types of lesions (range, 2–103; IQR, 2.2–18; $P < .01$, Kruskal-Wallis). Nine patients (18%) had hydrocephalus (enlarged cerebral ventricles), and 5 (12%) had cortical atrophy.

Number of bands on immunoblot

Sera from all 49 patients reacted to at least 2 bands. Sera from 23 patients (47%) reacted to all 7 bands. The median number of reactive bands was 6.0 (IQR, 3.5–7.0). Positive reactions to GP42–39 were present in all cases, to GP24 in 46 cases (94%), and to the other diagnostic bands in 30–37 cases (61%–78%).

Immunoradiologic correlation

Reaction to all 7 bands was associated with >3 lesions on CT (19/23 vs. 6/26, $P < .0001$). This relationship was seen both in patients with only cystic lesions (7/10 vs. 3/18, $P = .01$) and in those with enhancing lesions (12/15 vs. 1/6, $P = .01$).

More patients with enhancing lesions reacted to all 7 bands than did patients with only cysts. Reactions to ≥4 bands were present for all 9 patients with only enhancing lesions and for 19 of the 28 patients with only cystic lesions ($P = .06$). There was no significant difference in the median number of reacting bands between patients with only cystic lesions (6) and those with enhancing lesions (7). The GP13 band was significantly more frequent in patients with enhancing lesions (8/9) than in patients with cysts (14/28, $P = .04$; patients with both lesions are excluded from analysis). Neither hydrocephalus nor cortical atrophy was associated with either the number of reactive bands or the reaction to any specific band.

Posttreatment evolution

Immunoblot assays were done for the 49 study patients 3 months after therapy. Forty-four, 42, and 41 had immunoblots at 6, 9, and 12 months, respectively.

All 49 patients were examined by CT 3 months after treatment. At this examination, 17 patients did not exhibit active lesions and were considered (radiologically) cured.

Thirty-six patients had a second follow-up CT scan at 1 year. Six patients (17%) had changed CT status between 3 months and 1 year after treatment. Four cleared their active lesions and were considered cured. Two others, who had no active lesions on their 3-month CT scans, showed 1 active lesion each on the subsequent scan.

Early posttreatment increase in the number of bands

Of the 26 patients with ≤6 reactive bands at baseline, 23 had cystic lesions and 3 had only enhancing lesions. In 18 of the 23 patients with cysts, there was an increase in the number of reactive bands in assays on days 7 and 14, whereas no increase was seen in the 3 patients with only enhancing lesions ($P = .02$). The increase was significant in patients who received 14 days of albendazole therapy ($P = .02$) but not in those who received only 7 days ($P = .47$).

There was no significant association between an early increase in the number of bands and cure on CT at 3 months (8/10 vs. 8/13, $P = .20$). However, there was a trend between this increase in bands during the first 2 weeks and cure on CT by 1 year (6/6 vs. 5/9, $P = .13$).

Decrease in number of bands at 3 months after treatment

Most patients whose sera reacted to all 7 bands at baseline had the same immunoblot result at 3 months (20/23, 87%). At 3 months after therapy, 3 of the 17 cured patients had a decrease of at least 2 bands (compared with baseline) versus only 1 of the 32 noncured patients ($P = .11$, table 1). This patient became cured at 1 year. None of the patients became seronegative at 3 months.

Seroconversion to negative at 1 year after treatment

Of the 41 patients who had immunoblot assays done for a full year after treatment, only 3 (7%) became seronegative. One of them became seronegative at 6 months and 2 at 9 months. These 3 patients were considered cured at their 3-month CT scans; 2 of them underwent CT at 1 year and continued to be free of lesions. The 3 patients all had baseline immunoblots reacting to ≤3 bands. None of the cured patients whose baseline immunoblots reacted to ≥4 bands became seronegative. At 1 year after therapy, 12 (32%) of 38 patients showed a decrease of at least 2 bands, including 5 patients who still had active lesions on both their 3-month and l-year follow-up CT scans (table 1).

Discussion

In this study, most NCC patients remained seropositive for at least 1 year after successful antiparasitic therapy. However, in 3 cases, the immunoblots became negative before 1 year. Seroconversion to negative occurred as early as 6 months after therapy and predicted patient cure. The study population was systematically followed, and CT examinations were done irrespective of clinical status, so most biases inherent to therapeutic follow-up studies [9] were avoided.

In community surveys, most seropositive persons are asymptomatic, usually reacting to 1–3 bands [10, 11]. Our study population consisted only of patients with cerebral infections clearly visible on CT, and sera from almost half of the patients (23/49, 47%) reacted to all 7 bands. Patients reacting to all 7 bands have more severe disease than those reacting to ≤6 bands. In a previous study, patients with more lesions had higher antibody levels measured by ELISA [12].

As was predicted, patients with cystic lesions had an early increase in the number of reactive bands, presumably resulting from antibody formation against newly exposed antigens [8]. This was mainly evident in patients receiving albendazole for 2 weeks. This increase did not correlate with increased cure rates; the reason for this discordance is not clear. Enhancing lesions are already degenerating [13], so therapy should have little effect on the immune response.

Most cured patients whose sera reacted to all 7 bands at baseline had the same result at 1 year, suggesting that a strong response persists over time despite cure. Conversely, both a decrease in the number of bands after therapy and seroconversion during the first year were (albeit with small numbers) predictive of cure on CT.

Persistent seropositivity in cured patients may be due either to sustained stimulation by lesions missed by CT scan or to residual circulating antibodies. The reportedly high sensitivity of cerebral CT scan for cerebral cysticercosis has been questioned [14, 15]. In our series, 2 patients who were presumed cured at 3 months each exhibited 1 active lesion on

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their 1-year follow-up scan. Whether these lesions were simply missed by the previous scan, were undetectable and grew after treatment, or represent a new infection is not answerable at present. Reinfection, however, seems unlikely, since the patients lived in a zone without endemic *T. solium*, and no evidence of intestinal tapeworm infection was found in their families.

Serologic evaluation will only rarely help in determining care after treatment for NCC because persistent positive immunoblot results do not necessarily indicate active infection. However, rare cases may have early antibody disappearance in relation to cure.

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Table 1

Evolution of serologic characteristics of neurocysticercosis after drug treatment

	CT diagnosis at 3 months		
Immunoblot	**Cured***	**Not cured**	***p***
More bands in first 14 days†	8/10	8/13	.31
At least 2 fewer bands at 3 months	3/17	1/32	.11
At least 2 fewer bands at 1 year‡	7/12	5/26	.02
Became seronegative at 1 year§	3/13	0/28	.03

NOTE. Data are no. of patients/*n*. CT, computed tomography.

* No active lesions (cysts or nodular enhancing lesions).

† 23 patients with cysts and <7 bands on baseline immunoblot.

‡ 38 patients with immunoblot control assays at 1 year.

§ 41 patients with immunoblot control assays at 1 year or later.